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Quantitative assessment of left ventricular perfusion defects using real-time three-dimensional myocardial contrast echocardiography

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Quantitative assessment of perfusion defects with myocardial contrast echocardiography can be a valuable tool in the evaluation of patients with coronary artery disease. However, the use of 2-dimensional echocardiography for this purpose is limited to a restricted number of imaging planes. Real-time 3-dimensional echocardiography (RT3D) is a novel technique that provides instantaneous volumetric images. The aim of this study was to validate the use of RT3D for the quantitative assessment of myocardial perfusion defects in a model of acute coronary occlusion. To this end, 20 sheep underwent acute ligation of the left anterior descending (n = 14) or the posterior branch of the circumflex (n = 6) artery under general anesthesia. The RT3D images were obtained after left atrial injection of the contrast agent EchoGen (perflenapent emulsion; 0.8-1 mL). Evans blue dye was injected into the occluded coronary artery for subsequent anatomic identification of underperfused myocardium. The mass of the entire left ventricle and of the

underperfused myocardial region were measured after death. Blinded off-line calculation of left ventricular (LV) mass and perfusion-defect mass from RT3D images were performed using an interactive aided-manual tracing technique. Total LV mass ranged from 68 to 141 g (mean ± SD: 92 ± 24 g). The mass of the perfusion defect ranged from 0 to 43 g (mean ± SD: 16 ± 9 g) or 0 to 36% of total LV mass (mean ± SD: 18% ± 9%). The RT3D estimation of total LV mass strongly correlated with the anatomic measurement (*r* = 0.91; y = −2.54 + 1.04*x*; standard error of the estimate [SEE] = 11.9 g). The RT3D calculation of the mass of underperfused myocardium also strongly correlated with the anatomic measurement, both in absolute terms (*r* = 0.96; *y* = 2.01 + 0.87*x*; SEE = 2.2 g) and when expressed as percentage of total LV mass (*r* = 0.96; *y* = 0.11 + 1.02*x*; SEE = 2.8%). Hence, RT3D with myocardial contrast opacification accurately predicts the amount of underperfused myocardium in an animal model of acute coronary occlusion. This technique may therefore be useful for the quantitative assessment of myocardial perfusion defects in patients with coronary artery disease. (J Am Soc Echocardiogr 2002;15:206-13.)

Conventional 2-dimensional (2D) echocardiography is an established and extremely useful tool for the evaluation of patients with ischemic heart disease, largely because of its ability to provide important diagnostic and prognostic information regarding global and regional left ventricular (LV) function, valvular abnormalities, and intracardiac pressures. In addition, recent advances in cardiac ultrasound have paralleled the development of gas-filled microbubbles that reflect ultrasound during their passage through the coronary microcirculation to allow the assessment of myocardial perfusion. [1]

However, quantification of wall-motion abnormalities and myocardial perfusion with conventional echocardiography is restricted to the use of a few standard nonparallel views, which are assumed to be representative of the whole left ventricle. This assumption leads to an incomplete appreciation of the spatial extent of myocardium involved in the disease process, especially when the LV architecture is distorted. For example, several studies using myocardial contrast echocardiography (MCE) have demonstrated its capacity to assess areas “at risk” during coronary occlusion[2] [7] and infarct size after reperfusion. [8] [11] However, because most of these studies were performed using single or combined tomographic planes,[12] no truly quantitative measurement of the spatial extent of “at risk” or infarcted myocardium could be derived.

Real-time 3-dimensional echocardiography (RT3D) is a relatively novel technique that provides volumetric images without electrocardiography or respiratory gating. [13] [14] The entire volumetric data are obtained during a single image acquisition, circumventing the need for image reconstruction from 2D image sets. The use of this technique in combination with the injection of contrast agents for the evaluation of myocardial perfusion has not yet been investigated. Therefore, the aim of this study was to develop and validate the methodology to allow the use of RT3D for the quantitative assessment of underperfused myocardium.

Methods

Animal preparation

Twenty Dorset hybrid juvenile sheep were studied. All operative and animal management procedures were approved by the Animal Care and Use Committee of the National Heart, Lung and Blood Institute. Preoperative and intraoperative animal management and husbandry methods have been described in

detail elsewhere.[15] [16] Anesthesia was induced with intravenous sodium pentobarbital (25 mg/kg) and maintained with 1% to 2% isoflurane with oxygen. The animals were ventilated via an endotracheal tube using a volume-cycled ventilator. A Swan-Ganz catheter positioned in the pulmonary artery via the femoral vein; another catheter was positioned in the right common femoral artery for monitoring systemic arterial pressure and blood gases. These 2 catheters were interfaced with a physiologic recorder (ES 2000, Gould Inc, Cleveland, Ohio) using fluid-filled pressure transducers (model PD23 ID, Gould Statham, Oxnard, Calif). A catheter was positioned in the left atrium for contrast injection. Arterial blood gases and pH were maintained within physiologic ranges.

After cardiopulmonary bypass was instituted, either the artery comparable to the human mid-left anterior descending coronary artery (n = 14) or the obtuse marginal/posterior LV coronary artery (n = 6) was selected for occlusion. The myocardium was preconditioned by occluding the artery for 3 to 5 minutes on 2 occasions with a snare, followed by reperfusion for the period of visible reactive hyperemia. Rhythm disturbances were managed with lidocaine, metoprolol, bretyllium, procainamide, and/or electrical cardioversion. After 20 to 30 minutes for hemodynamic and rhythm stabilization, the animal was weaned from cardiopulmonary bypass with pulmonary arterial wedge pressure monitoring and, subsequently, echocardiographic studies were performed.

Real-time 3-dimensional echocardiography

A commercially available ultrasound unit (Volumetrics Medical Imaging, Model 1, Durham, NC) was used for epicardial RT3D image acquisition. This unit—based on the concept of receive mode parallel processing—scans 20 pyramidal volumes per second at a depth of 14 cm. Each volume contains 4096 scan lines, which are spaced approximately 1 degree apart in azimuth and in elevation.[13] [14] A 2.5-MHz matrix-array transducer was used during image acquisition. The RT3D images were obtained after coronary occlusion and during stable myocardial opacification after left atrial injection of EchoGen (Sonus Pharmaceuticals, Bothell, Wash). A standoff was positioned between the transducer and the LV apex to allow inclusion of the entire left ventricle in the 2 available B scans oriented at 90 degrees of each other. The acquired data were stored on optical disks for off-line processing and analysis.

Myocardial contrast echocardiography

EchoGen is an emulsion of 2% dodecafluoropentane (C5F12) molecules. The liquid droplets of EchoGen undergo a phase conversion to become microbubbles with a mean size of 2 to 5 μm.[17] The microbubbles circulate in the intravascular space and the gas-liquid interface enhances the intrinsic backscatter of blood providing enhanced gray scale. In each animal, 0.8 to 1 mL of the contrast agent was injected into the left atrium.

Anatomic perfusion-defect quantification

Each animal was killed with intracardiac potassium chloride under general anesthesia. The heart was subsequently excised and the corresponding coronary artery was cannulated at the site of its occlusion. Evans blue dye was infused through the catheter positioned in the occluded coronary artery. Both atria, the right ventricular free wall, the conal papillary muscle, the septal tricuspid valve leaflet, the semi-lunar valves, and the mitral valve apparatus were excised. The entire left ventricle was weighed, and after dissection of the area delineated by Evans blue dye, the weight of the underperfused myocardium was determined.

Measurements of LV mass and perfusion-defect mass from RT3D images

Calculation of LV mass and perfusion-defect mass from RT3D images were performed by an observer, unaware of the anatomic findings, using an interactive-aided manual tracing technique based on a Silicon Graphics workstation (Mountain View, Calif) with customized software. The design of the system is based on the operator's ability to trace and edit the endocardial and epicardial surfaces on any arbitrary slice through the volumetric image and have a visual rendering of the corresponding LV surfaces reconstructed. This gives the operator immediate feedback as to how the rendered LV shape is developing with each added data point.[18] Once the process of endocardial and epicardial tracing is completed, the system provides a rotatable 3-dimensional (3D) rendering of both surfaces from which the volume of LV myocardium is instantaneously calculated by subtracting the volume within the endocardial tracing from the volume within the epicardial tracing (Figure 1, *B*).

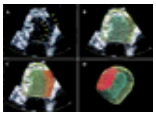

Fig. 1. Representative example of methodology used to quantitatively assess mass of underperfused myocardium from RT3D images in sheep with acute occlusion of circumflex coronary artery. **A,** Tomographic view derived from volumetric image showing area of myocardium devoid of contrast opacification (*arrows*). **B,** 3-dimensional rendering of left ventricular (LV) endocardial (in green) and epicardial (in yellow) surfaces generated by computer, based on operator's tracing. Area between both surfaces corresponds to myocardial volume, which is used to calculate myocardial mass. **C,** Rendering of LV region without contrast opacification generated by computer, based on operator's tracing of corresponding endocardial surface. Red area represents volume used to calculate mass of underperfused myocardium. After tracing is completed, volumetric image can be freely rotated to examine 3-dimensional appearance of LV endocardial and epicardial surfaces and underperfused myocardium, as shown in **D.**

The amount of myocardium affected by coronary occlusion was measured by tracing the LV endocardial surface devoid of myocardial opacification. The software extrapolates the tracing to the epicardial surface and calculates the volume of underperfused myocardium (Figure 1, *C* and *D*). Mass was then determined by multiplying the myocardial volume, calculated as described previously, by a conversion factor of 1.05 gm/cc, which corresponds to the density of the myocardium.

Statistical analysis

Data are presented as mean ± SD. Two means were compared by paired or unpaired Student *t* test, as appropriate. Relations between 2 variables were assessed by means of Pearson product moment correlation coefficient and by linear regression analysis. Statistical tests of interaction (testing equality of slopes and intercepts within a multivariate linear regression model) were used to compare anatomic and RT3D measurements in different vascular territories.

Results

Immediately after injection, contrast medium was observed in the LV cavity, followed by myocardial opacification within 1 minute and throughout the period of image acquisition. The myocardium subtended by the occluded coronary artery was distinctly seen on RT3D images as a region devoid of contrast opacification (Figure 1, *A*), which permitted a clear separation of healthy from underperfused myocardium for the purpose of quantification of myocardium “at risk.”

Anatomic measurements of total LV mass ranged from 68 to 141 g (mean ± SD:92 ± 24 g), whereas the RT3D calculation of LV mass ranged from 64 to 140 g (mean ± SD: 94 ± 28 g; $P = .62$ vs anatomic measurements). A strong linear relation was observed between RT3D estimation of total LV mass and

the corresponding anatomic measurements (r = 0.91) (Figure 2, *top panel*). The mean difference between RT3D and anatomic measurements was 1.32 ± 11.71 g (Figure 2, *bottom panel*).

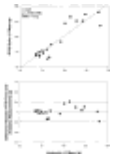

Fig. 2. Relation between anatomic and RT3D measurements of total left ventricular (LV) mass. *Top panel* shows correlation between measurements obtained with 2 techniques. *Bottom panel* shows Bland and Altman plot of difference between anatomic and RT3D LV mass as function of anatomic mass; values above zero line represent instances in which RT3D mass was greater than anatomic mass; *solid and dashed lines* indicate mean ± 2 SD of difference, respectively.

Anatomic measurements of underperfused myocardium ranged from 0 to 43 g (mean ± SD: 16 ± 9 g) or 0% to 36% of total LV mass (mean ± SD: 18% ± 9%). RT3D calculation of the mass of underperfused myocardium ranged from 0 to 37 g (mean ± SD: 16 ± 8 g; P = .83 vs anatomic measurements) or 0% to 41% of total LV mass (mean ± SD: 19% ± 10%; P = .43 vs anatomic measurements). A strong correlation was found between the RT3D calculation of the mass of underperfused myocardium and the anatomic measurements, expressed both in absolute terms (r = 0.96) (Figure 3, *top panel*) and in percentage terms (r = 0.96) (Figure 4, *top panel*).

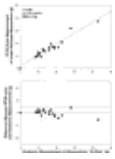

Fig. 3. Relation between anatomic and RT3D measurements of underperfused myocardial mass. *Top panel* shows correlation between measurements obtained with 2 techniques. *Bottom panel* shows Bland and Altman plot of difference between anatomic and RT3D underperfused left ventricular mass as a function of true anatomic mass; values above zero line represent instances in which RT3D mass was greater than anatomic mass; *solid and dashed lines* indicate mean ± 2 SD of the difference, respectively.

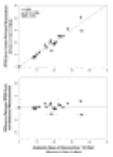

Fig. 4. Relation between anatomic and RT3D measurements of underperfused myocardial mass expressed as percentage of total left ventricular mass. *Top panel* shows correlation between percentage measurements obtained with 2 techniques. *Bottom panel* shows Bland and Altman plot of difference between percentage anatomic and RT3D underperfused left ventricular mass as function of anatomic mass measurements; values above zero line represent instances in which percentage RT3D mass was greater than anatomic mass; *solid and dashed lines* indicate mean ± 2 SD of difference, respectively.

The mean differences between RT3D and anatomic measurements of mass of underperfused myocardium were −0.1 ± 2 g (Figure 3, *bottom panel*) or 0.5% ± 3% of total LV mass (Figure 4, *bottom panel*).

Statistical tests of interaction showed no significant difference in the linear relation between RT3D and anatomic measurements for the anterior versus the posterior vascular territories (ie, ligation of the LAD vs the posterior branches). Accordingly, the difference between anatomic and RT3D measurements of underperfused myocardial mass were similar for the anterior and posterior vascular territories (0.7 ± 3 g vs 1.2 ± 2 g, respectively, P = .12; or 0.1% ± 3% vs 1.6% ± 2% of total LV mass, respectively, P = .29).

Discussion

During the early stages of MCE investigation, accurate assessments of the area “at risk,” ie, the amount of underperfused myocardium during acute coronary occlusion, were performed and validated using technetium autoradiography.[4] [5] Most of these studies were performed using single tomographic planes, which may be representative of the spatial extent of underperfused myocardium but prevents a truly quantitative assessment.

Subsequently, the area “at risk” for infarction after acute coronary occlusion could be determined accurately by MCE for the entire left ventricle using 3D reconstruction of multiple tomographic slices. However, the acquisition of the cross-sectional images was not simultaneous and required respiratory gating, to avoid cardiac translation, and selection of cycles with a predefined length to avoid misregistration. [12] Despite these shortcomings, using an open-chest animal model of acute myocardial infarction, Yao et al[19] showed a good correlation between percentage of LV mass involved in dysfunction and percentage of LV mass involved in infarction, comparing 3D imaging reconstruction from 2D images with infarct mass defined by triphenyltetrazolium staining. By using a similar approach, Sapin et al[20] found good correlation between the 3D echocardiographic measurements of dyssynergic endocardial surface area with infarct mass. It was also demonstrated in patients that the extent of dysfunctional mass obtained through 3D reconstruction of transesophageal 2D images correlated well with contrast magnetic resonance imaging, used as a reference standard for infarcted tissue detection.[21] The lack of overestimation of infarct size based on the 3D quantification of dysfunctional mass, in contrast with previous 2D observations, is a consistent feature of those publications.[19] [21] More recently, Yao et al[22] used an animal model and 3D reconstruction from 2D images to estimate myocardial mass after coronary ligation and intravenous injection of contrast. Strong correlations were obtained between the extent of perfusion defects by 3D echocardiography and anatomic measurements of the myocardial mass “at risk,” anatomic infarct mass, and salvaged mass after reperfusion.

In this investigation, we tested the accuracy of RT3D quantification of underperfused myocardium using customized software specifically designed for quantitative measurements of LV mass. This technique has important potential advantages over other noninvasive methods. First, the instantaneous acquisition of a pyramidal volume of information does not require electrocardiographic or respiratory gating, thus overcoming the limitations related to the sequential acquisition of 2D images for subsequent reconstruction. In addition, the customized software allows the operator to rapidly obtain a truly 3D quantitative assessment of underperfused myocardium, taking full advantage of the entire data set.

In our study, we found that the actual mass of underperfused myocardium can be accurately quantified with RT3D in the setting of acute coronary occlusion. Thus, we observed an excellent correlation between the calculated mass of myocardium devoid of contrast opacification and anatomic measurements of myocardium subtended by the occluded coronary artery, without systematic overestimation or underestimation. Further, RT3D provided accurate measurements of total LV mass and of the percentage of myocardium affected by the acute coronary occlusion, independently of the vascular territory undergoing acute occlusion.

These findings may have meaningful clinical implications. Thus, the use of a noninvasive methodology that permits accurate quantitative assessment of myocardium “at risk” would be useful for the prognostication and serial evaluation of patients showing symptoms of acute myocardial infarction. Most important, myocardium “at risk” does not actually imply infarcted myocardium, but rather the amount of myocardium that would become infarcted in the absence of spontaneous lysis or reperfusion therapy. Early achievement of infarctrelated artery patency is the primary goal in the initial treatment of acute myocardial infarction to limit myocardial infarct size, decrease LV dysfunction, and ultimately improve survival.[23] In this context, a method capable of defining the amount of underperfused myocardium in absolute, and percentage values would be extremely helpful in assessing changes in myocardial perfusion before and after the patency of the infarct-related artery is achieved. Because MCE is capable of establishing myocyte integrity by defining capillary perfusion,[24] its combination with RT3D has the potential to assess microcirculatory changes derived from interventions

at the level of the epicardial coronary arteries.

Further, the strong indexes of agreement between RT3D and anatomic measurements of underperfused myocardium suggest that the former may also be used accurately for the quantitative assessment of regional wall-motion abnormalities, although this hypothesis was not directly tested in our study. Because wall-motion abnormalities after acute myocardial infarction evolve as a consequence of recovery of “stunned” but viable myocardium and changes in LV geometry from remodeling, the repeated quantitative assessment of wall motion would be useful for the study of the evolution of regional and global LV function after an acute ischemic event.

Certain limitations of our study must be acknowledged. First, the epicardial acquisition of echocardiographic images combined with the injection of a contrast agent into the left atrium do not faithfully represent the clinical context in which this methodology may be most useful. Hence, the results of the present study should not be viewed as a demonstration of the clinical applicability of this technique. Instead, they intend to describe a novel method of quantitative measurement of underperfused myocardium in the setting of ideal circumstances to permit its appropriate validation. Further studies are therefore needed to determine the use of this methodology in the clinical arena. Second, the current spatial resolution of the RT3D system is below that of the commercially available 2D echocardiographs. This may negatively affect the usefulness of RT3D in patients with acute myocardial infarction. Refinements in the system capabilities therefore will be necessary for its wide application to cardiac patients. Third, in our study, the myocardial perfusion defect by RT3D was defined as the amount of myocardial mass devoid of contrast enhancement after intra-atrial injection of contrast, whereas the corresponding anatomic mass was defined by the amount of stained myocardial mass after infusion of Evans blue dye at the site of coronary artery occlusion. In theory, the injection of dye into the coronary artery, distal to the ligation, may stain more myocardial tissue than it does when it is injected into the left atrium and could, thus, lead to overestimation of the anatomic mass of underperfused myocardium.[21] In addition, the myocardial perfusion defect was defined in vivo by MCE, whereas the dye injection was performed after the heart was removed. Despite these differences in methodology, we found a strong correlation between the 2 measurements. Finally, it must be noted that our findings refer to a specific ultrasound contrast agent that is not commercially available. Therefore, these findings must be reproduced with other agents available for human use before this technique can be applied to the clinical arena.

In conclusion, this study describes a novel methodology for the quantitative assessment of underperfused myocardium using RT3D images obtained after injection of an ultrasonic contrast agent. These measurements accurately predicted the anatomic mass of myocardium subtended by an occluded coronary artery and may be useful for the initial and serial evaluation of myocardial damage in patients with acute myocardial infarction.

References

1. Kaul S. Myocardial contrast echocardiography: 15 years of research and development. Circulation 1997;96:3745-60. Citation

2. Tei C, Sakamaki T, Shah PM, Meerbaum S, Shimoura K, Kondo S, et al. Myocardial contrast echocardiography: a reproducible technique of myocardial opacification for identifying regional perfusion deficits. Circulation 1983;67:585-93. Abstract

3. Kemper AJ, O'Boyle JE, Cohen CA, Taylor A, Parisi AF. Hydrogen peroxide contrast echocardiography: quantification in vivo of myocardial risk area during coronary occlusion and of the necrotic area remaining after myocardial reperfusion. Circulation 1984;70:309-17. Abstract

4. Kaul S, Pandian NG, Okada RD, Pohost GM, Weyman AE. Contrast echocardiography in acute myocardial ischemia: I, in vivo determination of total left ventricular “area at risk.” J Am Coll Cardiol 1984;4:1272-82. Abstract

5. Kaul S, Glasheen W, Ruddy TD, Pandian NG, Weyman AE, Okada RD. The importance of defining left ventricular area at risk in vivo during acute myocardial infarction: an experimental evaluation with myocardial contrast two-dimensional echocardiography. Circulation 1987;75:1249-60. Abstract

6. Villanueva FS, Glasheen WP, Sklenar J, Kaul S. Assessment of risk area during coronary occlusion and infarct size after reperfusion with myocardial contrast echocardiography using left and right atrial injections of contrast. Circulation 1993;88:596-604. Abstract

7. Grayburn PA, Erickson JM, Escobar J, Womack L, Velasco CE. Peripheral intravenous myocardial contrast echocardiography using a 2% dodecafluoropentane emulsion: identification of myocardial risk area and infarct size in the canine model of ischemia. J Am Coll Cardiol 1995;26:1340-7. Abstract

8. Firschke C, Lindner JR, Wei K, Goodman NC, Skyba DM, Kaul S. Myocardial perfusion imaging in the setting of coronary artery stenosis and acute myocardial infarction using venous injection of a second-generation echocardiographic contrast agent. Circulation 1997;96:959-67. Abstract

9. Kemper AJ, O'Boyle JE, Cohen CA, Taylor A, Parisi AF. Hydrogen peroxide contrast echocardiography: quantification in vivo of myocardial risk area during coronary occlusion and of the necrotic area remaining after myocardial reperfusion. Circulation 1984;70:309-17. Abstract

10. Villanueva FS, Glasheen WP, Sklenar J, Kaul S. Characterization of spatial patterns of flow within the reperfused myocardium by myocardial contrast echocardiography: implications in determining extent of myocardial salvage. Circulation 1993;88:2596-606. Abstract

11. Villanueva FS, Camarano G, Ismail S, Goodman NC, Sklenar J, Kaul S. Coronary reserve abnormalities in the infarcted myocardium: assessment of myocardial viability immediately versus late after reflow by contrast echocardiography. Circulation 1996;94:748-54. Abstract

12. Linka AZ, Ates G, Wei K, Firoozan S, Skyba DM, Kaul S. Three-dimensional myocardial contrast echocardiography: validation of in vivo risk and infarct volumes. J Am Coll Cardiol 1997;30:1892-9. Abstract

13. von Ramm OT, Smith SW. Real time volumetric ultrasound imaging system. J Digit Imaging 1990;3:261-6. Abstract

14. Smith SW, Pavy HG, von Ramm OT. High-speed ultrasonic volumetric imaging system: part I, transducer design and beam steering. IEEE Trans Ultrasonics Frequency Control 1991;38:100-8.

15. Jones M, Barnhart GR, Chavez AM, Jett GK, Rose DM, Ishihara T, et al. Experimental evaluation of bioprosthetic valves implanted in sheep. In: Cohn LM, Gallucci V, editors. Cardiac bioprostheses. New York: Yorke Medical Books; 1982. p. 275-92.

16. Tamura K, Jones M, Yamada I, Ferrans VJ. A comparison of failure modes of glutaraldehyde-treated versus antibiotic-preserved mitral valve allografts implanted in sheep. J Thorac Cardiovasc Surg 1995;110:224-38. Abstract

17. Grayburn P. Perflenapent emulsion (EchoGen): a new long-acting phase-shift agent for contrast echocardiography. Clin Cardiol 1997;20(10 Suppl 1):I12-8. Abstract

18. Schmidt MA, Ohazama CJ, Agyeman KO, **Freidlin** RZ, Jones M, Laurienzo JM, et al. Real-time three-dimensional echocardiography for measurement of left ventricular volumes. Am J Cardiol 1999;84:1434-9. Abstract

19. Yao J, Cao QL, Masani N, Delabays A, Magni G, Acar P, et al. Three-dimensional echocardiographic estimation of infarct mass based on quantification of dysfunctional left ventricular mass. Circulation 1997;96:1660-6. Abstract

20. Sapin PM, Clarke GB, Gopal AS, Smith MD, King DL. Validation of three-dimensional echocardiography for quantifying the extent of dyssynergy in canine acute myocardial infarction: comparison with two-dimensional echocardiography. J Am Coll Cardiol 1996;27:1761-70. Abstract

21. De Castro S, Yao J, Magni G, Cacciotti L, Trambaiolo P, De Santis M, et al. Three-dimensional echocardiographic assessment of the extension of dysfunctional mass in patients with coronary artery disease. Am J Cardiol 1998;81:103G-6G. Abstract

22. Yao J, Teupe C, Takeuchi M, Avelar E, Sheahan M, Connolly R, et al. Quantitative 3-Dimensional contrast echocardiographic determination of myocardial mass at risk and residual infarct mass after reperfusion: experimental canine studies with intravenous contrast agent NC100100. J Am Soc Echocardiogr 2000;13:570-81. Full Text

23. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded? Circulation 1989;79:441-4. Citation

24. Camarano G, Ragosta M, Gimple LW, Powers ER, Kaul S. Identification of viable myocardium with contrast echocardiography in patients with poor left ventricular systolic function caused by recent or remote myocardial infarction. Am J Cardiol 1995;75:215-9. Abstract